that this Information Disclosure Statement has been considered by the Examiner. Appropriate notification is requested.

Regarding the previous objections to the disclosure because of informalities, Applicants thank the Examiner for withdrawing the objections. Applicants note that the previously proposed amendments made to page 25, line 26 and page 24, line 17 were not entered due to errors in the instructions provided by Applicants. In the present amendment, page 24, line 21 is amended in a further effort to correct a patent, minor error of typographical character.

The Provisional Double Patenting Rejections (Paragraphs 5, 8, and 12 of Paper No. 8)

With respect to the provisional rejection of Claims 1-19 under 35 U.S.C. § 101 over copending application Serial Nos. 08/470,107 and 08/459,147, we note that this rejection has been transferred from Claims 1-19 to Claims 10-23. In this regard, Applicants find it appropriate to review at this time, the standard to support a rejection for double patenting under 35 U.S.C. § 101.

The test to determine if two inventions are the same is "whether one of the claims being compared could be literally infringed without literally infringing the other". If this is possible, the claims do not define identically the same invention. In re Vogel, 422 F.2d 438 (441); 164 U.S.P.Q. 619 (622) (C.C.P.A. 1970). We submit that in applying this test to the claims of the three cases, that the above enunciated test could in application cause a determination that the inventions are not the same. Therefore, the rejection fails.

Regarding the provisional rejection of Claims 11, 13 and 18-23 under the judicially created doctrine of obviousness-type double patenting over copending application Serial No. 08/357,084, it is still Applicants' position that the claims of the present application, as amended, are directed to a separate patentable invention under the provisions of 37 C.F.R. § 1.601(n). However, Applicants note the Examiner's acknowledgment that Applicants would consider the filing of a terminal disclaimer sanctioned by 37 C.F.R . § 1.321 if appropriate at the time claims of the present case are found allowable but for this issue.

The Rejections under 35 U.S.C. § 112, Second Paragraph (Paragraphs 6 and 13 of Paper No. 8)

Applicants thank the Examiner for withdrawing the rejection of Claims 1 to 19 under 35 U.S.C. § 112, second paragraph.

Claims 22 and 23 stand rejected under 35 U.S.C. § 112, second paragraph, for purportedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner states that the claims are indefinite in the recitation of "additional effective glycoprotein".

Claim 22 has been amended to delete the phrase "additional effective glycoprotein". Claim 23 has been amended to delete "and glycoprotein D". These amendments are intended to clarify what is intended to be the claimed subject matter, and are not meant to modify the scope of the claims in any manner. Applicants believe that these amendments address and rectify the issue of indefiniteness. Applicants, therefore, respectfully request that this rejection be withdrawn.

The Rejection under 35 U.S.C. § 112, First Paragraph (Paragraphs 9 and 10 of Paper No. 8)

Claims 10, 12, 13-17 and 20-23 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is purportedly enabling "only for claims limited to a vaccine comprising a truncated, membrane free glycoprotein D polypeptide of the herpes simplex virus and a method of producing the vaccine." Particularly, the Examiner objects to the inclusion of glycoprotein C, glycoprotein B, glycoprotein A, glycoprotein E, and mixtures of glycoproteins. Applicants respectfully traverse.

It appears to be the Examiner's position that while the specification shows sequencing and expression data for both glycoproteins D and C, challenge data is only presented in support of glycoprotein D, therefore, only glycoprotein D is enabled. Applicants respectfully point out that it is well established law that each and every embodiment need not be demonstrated in the specification so long as enough information is presented to provide a reasonable expectation of success in practicing the claimed invention.

The Examiner points out that Applicants have urged that challenge data is necessary in order to prove effectiveness of a vaccine. It is still Applicants' position that challenge data was necessary to establish the enabled "teachings" of the prior art and that the present case is distinguishable over that art in a patentable sense. Specifically, Applicants argued that challenge data was necessary to enable Watson, et al., *Science*, 218:381-384 (1982) (Watson) and Rose, et al., *Cell*, 30:753-762 (1982) (Rose). However, as pointed out throughout prosecution of this case and the cases from which this case descends, Watson discloses the expression of fusion

proteins, and Rose discloses a truncated glycoprotein G protein that could be folded into "an unusual confirmation". In both disclosures, there appeared to be doubt as to whether the disclosed peptides would be effective against a challenge. In particular, as repeatedly pointed out by Applicants, the authors in Watson declared that further experimentation was necessary to determine the capabilities of the fusion peptides. The authors in Rose were clearly perplexed by the folding patterns. Therefore, it was clear that challenge data was necessary for these particular cases in order to be sufficiently enabled to support the obviousness rejections.

Our urgings of the necessity of challenge data in order to enable a vaccine as claimed herein, establishes patentability of our vaccine over the art cited by the Examiner since Applicants have demonstrated at least one successful challenge in accordance with the claimed invention. Without the challenge data provided in the present specification, absent in the cited art, it would not have been obvious to one skilled in the art at the time the invention was made that the claimed vaccines and methods could be practiced with a reasonable expectation of success.

Therefore, in contrast, Applicants have provided enough disclosure to provide one skilled in the art with a reasonable expectation that the claimed invention could be practiced with success over the entire range. In particular, Applicants have provided at least one successful challenge from which the results of the remaining glycoproteins can be predicted. Moreover, in contrast to Watson and Rose, the present specification does not indicate any reason why all of the claimed glycoproteins would not provide protection similarly to glycoprotein D. Particularly, in the analysis of the expression of glycoprotein C, fusion peptides

were not prepared or expressed, nor were any strange folding patterns observed as indicated in the art requiring challenge data.

Additionally, Applicants have provided similarities between glycoprotein C and the protein which has been demonstrated to be successful as a vaccine, glycoprotein D. Namely, page 46, lines 19-28 show that sequence comparisons of glycoproteins C and F demonstrate that the carboxy-terminal transmembrane domains of these proteins are able to tolerate a large number of mutations in this area so long as the substituted amino acids are hydrophobic. These results are similar to those found for the glycoprotein D genes of HSV-1 and HSV-2. Another similarity is that all of the glycoproteins possess some type-common determinants (page 2, lines 29-32).

However, Applicants point out that the similarities between glycoprotein D and the other glycoproteins should not be in issue. The point emphasized is that there is no similarity between the glycoproteins of the present invention and those of the prior art which are either fusion proteins or peptides which were immediately demonstrated to have irregularities. Because the present glycoproteins can be distinguished from those of the prior art and because the present glycoproteins are presented in conjunction with at least one successful example of use as a vaccine, Applicants submit that each and every one of the presently claimed glycoproteins do not require challenge data to be enabled.

Moreover, Applicants have provided Declaration evidence in the line of cases from which this case descends, which verify the enablement of the claimed invention. Specifically, in Serial No. 08/171,858, filed 21 December 1993, an

Amendment was mailed by Applicants dated 21 July 1994 (approximately Paper No. 46 in that case) with appendices including: (1) a Declaration of John K. Rose in Support of Reply to Opposition by Chiron Corporation, (2) a (follow-up) Declaration of John K. Rose, Ph.D., and (3), a Statutory Declaration by David S. Secher, all enclosed herein as Exhibits A, B and C, respectively. Applicants again point out that these Declarants are not inventors of the present invention, and in fact, Dr. Rose is an author of one of the publications cited against the present invention by the Examiner.

Declaration of John K. Rose in Support of Reply to Opposition by Chiron Corporation

In the Declaration of John K. Rose in Support of Reply to Opposition by Chiron Corporation, paragraph 8 states:

> [O]ne of ordinary skill in the art could not have predicted that a successful vaccine that raises neutralizing (protective) antibodies against <u>in vivo</u> challenge by a pathogen could have been produced based essentially on a truncated, membrane-free derivative of a membrane-bound glycoprotein of the virus...

It is clear based on this language, that the Declarant viewed the invention as encompassing truncated, membrane-free derivatives of a membrane-bound glycoprotein of the virus, not limited to glycoprotein D.

Paragraph 9 of the same Declaration goes on to state:

> Based upon this pioneering demonstration with the herpes simplex vaccine model, their results provide a reasonable expectation that the system would be successful with other viral pathogens.

Applicants point out the term "pioneering" which indicates that the Declarant envisioned ground breaking and broad applications with this system "based

essentially on a truncated, membrane-free derivative of a membrane-bound glycoprotein of the virus" (paragraph 8 of the Declaration). Applicants, therefore, submit that this Declaration supports enablement of the claimed glycoproteins.

Declaration of John K. Rose, Ph.D.

In paragraph 13 of the (follow-up) Declaration of John K. Rose, Ph.D., Dr. Rose offers further explanation of the Declaration discussed above. Specifically, again, Dr. Rose refers to the invention as "based on a truncated, membrane-free viral glycoprotein" indicating that one skilled in the art does not consider the invention limited to glycoprotein D. Moreover, in Paragraph 13 of this Declaration, Dr. Rose explains that any reasonable expectations of success in using the disclosed system arose because the inventors "demonstrated that all of the technical challenges to successful vaccine production had been overcome". Applicants, therefore, submit that this Declaration supports enablement of the claimed glycoproteins.

Statutory Declaration by David S. Secher

Paragraph 11 of the Statutory Declaration by David S. Secher states:

> The scientific strength of this research resides in the use of a truncated version of a single glycoprotein from the rather complex model Herpes Simplex virus to confer protective immunity in the animal against the pathogen.

Applicants, point out that like Dr. Rose, Dr. Secher did not mention the use of glycoprotein D, but rather, refers generally to a truncated version of a glycoprotein. Applicants, therefore, submit that this Declaration supports enablement of the claimed glycoproteins.

Therefore, regarding the enablement of glycoproteins other than glycoprotein D, Applicants have met their burden of proof for enablement by providing an enabling disclosure, and further by providing supporting evidence which confirms the statements in the disclosure. Applicants respectfully point out that an Applicants' specification that discloses information on how to make and use the invention must be accepted unless the Patent Office provides sufficient reason to doubt the accuracy of the disclosure. If the Patent Office does present doubt to the accuracy of the disclosure, then such a rejection can be overcome by suitable proofs such as the submission of expert declarations. In re Marzocchi, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). In this case, assuming *arguendo* that the Patent Office raised a doubt to the accuracy of the specification, Applicants submit that this rejection has been overcome by the Declarations previously submitted in the history of this case and enclosed herein. Applicants, therefore, respectfully request that this rejection be withdrawn.

Regarding the mixtures of glycoproteins, Applicants have specifically pointed out where the specification provides support. For example, at page 48, lines 5- 9, the specification states that it is further believed that a vaccine which includes a mixture of gC and gD glycoproteins would be significantly more effective as a vaccine against HSV-1 and HSV-2 than one based upon either glycoprotein alone. However, Applicants also submit that this is only one specific example of the disclosed mixtures. Specifically, lines 10-12 of page 5 state that combinations of glycoproteins C and F could be used, and that other glycoproteins include glycoproteins A, B and E. Applicants believe that taken in context, the specification

explicitly states that all mixtures of the claimed glycoproteins are considered within the scope of the claimed invention.

Further regarding the mixtures of glycoproteins, Applicants point out that pages 14 and 15 of the Office Action, Paper 8, confirm that mixtures of glycoproteins "would have been obvious to one skilled in the art", in context of the obviousness rejection. Certainly, having established patentability herein over that art, it could not be contrarily argued properly that our own disclosure does not enable mixtures.

Applicants submit a detailed explanation below of why the prior publications do not disclose or make obvious the claimed invention, but point out that given the enabling present disclosure and the Examiner's own standards, mixtures are reasonably disclosed to one skilled in the art in the present application.

Given the above, Applicants submit that the present specification is enabling for the use of all of the claimed glycoproteins or mixtures thereof, as a vaccine against herpes virus. In light of this disclosure and consideration of the enclosed evidentiary Declarations, Applicants respectfully request withdrawal of the outstanding rejection.

With respect to paragraph 10 of Paper No. 8, Applicants now understand the issue of priority to be applied to the specific mixtures of glycoproteins, other than mixtures of glycoproteins C and D. Applicants respectfully traverse.

The Examiner does not seem to dispute that no substantive additions have been made to the specification at least since 9 March 1994, the filing date of Serial No. 06/588,170. Therefore, there does not seem to be an issue as to the priority

date of the present application, but simply whether or not, this case (or the parent cases) is enabled. In support of the assertion that this case is enabled, Applicants again submit that it is unreasonable to interpret the explicit disclosure of the mixture of glycoproteins C and D to exclude other mixtures. As discussed above, Applicants submit that one skilled in the art would understand that the specific example of combining glycoproteins C and D was made to point out the more general and obviously intended statement that any mixture of the disclosed glycoproteins are within the scope of the invention. As also discussed above, Applicants believe that page 5, lines 5-14, of the specification explicitly discloses the mixtures of Claim 20. Applicants, therefore, respectfully request that the Examiner regard this rejection properly as not one of priority, but one of enablement, and in consideration of the preceding remarks, withdraw the rejection.

The Rejection under 35 U.S.C. § 103 (Paragraphs 11, 14 and 15 of Paper No. 8)

Claims 10, 11, 13-15, 18 and 19 stand rejected under 35 U.S.C. § 103 as purportedly being unpatentable over Watson in view of Rose. Moreover, Claims 16 and 17 are rejected under 35 U.S.C. § 103 as purportedly being unpatentable over Watson in view of Rose and further in view of Kaufman, et al., *Mol. Cell Biol.*, 2(11):1304-1319 (1982) (Kaufman). Additionally, Claims 12 and 20-23 are rejected under 35 U.S.C. § 103 as purportedly being unpatentable over Watson and Rose in view of Chan, *Immunol.*, 49:343-352 (1983) (Chan). Applicants respectfully traverse.

Applicants begin with a discussion of the enclosed copy of a Declaration under 37 C.F.R. § 1.131 submitted in the parent to this case, Serial No. 08/357,084, (enclosed herein, as Exhibit D, without the appended documents filed with the original). This Declaration under 37 C.F.R. § 1.131 was first mailed 18 October 1995 with an Amendment in the parent case. In Paper 63 of that case, the Examiner challenged the Declaration which Applicants rebutted in the remarks submitted on 7 August 1996. A Notice of Allowance followed, dated 13 November 1996.

Applicants asserted, and assert herein, that the enclosed Declaration under 37 C.F.R. § 1.131 is fully sufficient to remove the various references cited herein, namely, Watson (and related Watson references referred to as "collective Watson references" discussed in detail below) as well as Rose, Kaufman and Chan. Thus, the rejections must and do fall.

In summary, the said declaration serves to comply with the true requirements of 37 C.F.R. § 1.131 by showing conception activity prior to July of 1982 followed by due diligence leading to an actual reduction to practice of the invention, in full satisfaction of 37 C.F.R. § 1.131. As all of the references cited by the Examiner have thus been removed, they cannot be considered as prior art to sustain the present invention.

However, we respond again, with respect to the cited references, and in particular the collective Watson references, as follows:

Various of the claims remain rejected as "unpatentable over Watson in view of Rose" or "Watson in view of Rose and further in view of Kaufman" or "Watson

in view of Rose and further in view of Chan". Previously in the prosecution history of the series of applications in the lineage of this application, we have addressed these rejections both individually and collectively, and have concluded that the so-called collective Watson references could very well be considered the primary references.

With reference to Watson, the Examiner states that Watson shows the "cloning and expression of the gene coding for herpes simplex virus type 1 glycoprotein D" and that antisera from such glycoprotein D can "neutralize infectivity of herpes simplex virus (HSV) type in an *in vitro* assay". It also appears to be the Examiner's position that given Applicants' usage of the term "comprising", somehow the claimed glycoproteins could encompass the fusion proteins of Watson. The Examiner further states that Rose teaches expression of secreted forms of integral membrane proteins and that Kaufman teaches the use of the DHFR minus cell as a host cell. Regarding Chan, the Examiner states that Chan suggests that glycoproteins C, D or a mixture of glycoproteins A and B have been implicated in cytotoxity and therefore may have some immunization effect. The Examiner concludes that based upon all of these teachings, "[i]t would have been expected... that the viral glycoproteins would be effective in generating immune responses which would be protective against HSV."

Initially, with regard to the Watson *Science* article, a detailed reading of the Watson article indicates that while Watson does provide the nucleotide sequence of the HSV-1 coding region, the only proteins <u>expressed</u> are <u>fusion proteins</u> which also contain amino acid sequences derived from the bacteriophage λCRO protein. Thus,

contrary to the Examiner's implication herein, Watson does not express nor produce the complete, intact and unassociated glycoprotein D molecule.

Regarding the Examiner's statement that Applicants also do not provide an intact molecule, but a truncated molecule, and further use the word "comprising", Applicants traverse. The cases cited by the Examiner state that the term "comprising" means that the claims must include at least the claimed subject matter and may further include other unrecited elements. This does not elevate the disclosure of Watson to disclose or suggest what is presently claimed. It is Applicants' position that Watson does not express the claimed glycoprotein but expresses a fusion protein, and therefore, does not include the minimum subject matter claimed by Applicants. These comments also apply to the Examiner's statements on page 12 of Paper 8 regarding the chimeric glycoprotein disclosed in Weiss, et al., *Nature*, 302:72-74 (1983). Moreover, it is Applicants' position that Watson does not provide any reasonable expectation of success in practicing the claimed invention; therefore, the term "comprising" is further irrelevant. This discussion is presented in greater detail below.

The Examiner's statement referring to Watson's "teachings" of neutralizing antisera, again this statement is extremely misleading and is incorrect in fact. First, none of the above was actually demonstrated by Watson. Watson merely makes reference to such work in the "background" section of their article. As such, Watson cannot be credited with "teaching" the above.

Applicants note that the Examiner applies the Watson reference under an obvious rejection and not as being anticipatory. However, Applicants point out that

since the critical elements to render the claimed invention obvious are not disclosed by Watson, combining Watson with general teachings in the art will still not support the rejection.

Next, the assertion that Applicants do not dispute that it is well known in the art that antiserum generated to glycoprotein D of herpes simplex virus can neutralize infectivity is simply not true. Applicants have disputed this point for the past thirteen years of prosecution of this case. However, it is certainly Applicants' point that regardless, the in vitro data of Watson is not indicative of what may result in vivo. Regarding this issue, while Watson does indicate that antiserum to various herpes glycoproteins can neutralize infectivity by HSV in vitro, nowhere in the Watson article is it demonstrated that antiserum produced in vivo is capable of neutralizing HSV infectivity in vivo.

The Examiner's statement (presumptively citing to page 381 of the Watson article) implies that antiserum directed against gD was produced in vivo and was shown to be capable of neutralizing HSV infectivity in vivo. This is absolutely incorrect. A detailed reading of the section cited by the Examiner indicates that monoclonal antibodies directed against the gD protein were obtained and the monoclonal antibodies themselves were passively transferred into mice. Thus, no antiserum was produced against the gD protein in vivo nor was any anti-gD antiserum tested for it ability to neutralize HSV infectivity in vivo.

Regarding the Examiner's statement that the term "monoclonal" is not in the claims, Applicants submit that such recitation is not necessary. The argument above is not necessarily presented to show the distinctions of the claimed subject matter

from that disclosed in Watson, but to show that one skilled in the art would not have a reasonable expectation that the teachings of Watson would be effective for the purposes of the claimed invention.

Concerning the "collective Watson references", Applicants note the Examiner's comment that the Watson patents are not under re-examination. However, as explained in further detail below, the substance of what is disclosed in Watson is in issue, and therefore must be reviewed.

During the prosecution of a parent application herein, namely, Serial No. 07/814,243 in an amendment filed by mailing on 19 April 1993, Applicants pointed out that the so-called Watson art should include not only the *Science* article cited by the Examiner herein but also two Watson patents (US 4,818,694 and 4,891,315). In an amendment filed on or about 10 November 1993 in that case, referring to an interview extended to Applicants' representatives on 28 October 1993, we pointed out that the three Watson references were discussed therein. Previously, and herein, we refer to all of these references as the "collective Watson references."

With particular reference to the Watson '315 patent, we note that although it contains a first filing date in the United States of 20 July 1982, there were also two continuations-in-part filed resulting in a final application filed 6 July 1983, i.e., just closely prior to the effective filing date herein of 30 August 1983. I have been informed, and believe, that the continuation-in-part applications added substantial subject matter. I draw particular attention to the subject matter in columns 43 and 44, and in particular Tables 4 and 5 that were added by the application filed on 6 July 1983. Certain other subject matter takes only the 25 October 1982 date.

In previous responses to Office Actions in applications throughout the lineage of the present application, Applicants have pointed out that the Watson *Science* article provides absolutely no challenge data. (The Science article is the reference used as a basis for this rejection). This is significant because Applicants have demonstrated herein the provision of an absolute protective effect upon challenge, which is the hallmark, indeed the necessity, of a vaccine that could expect to be ultimately commercially successful. Applicants further submit that only because Applicants have provided this successful challenge data, can they apply this data to the predictability of the remaining glycoproteins of the claimed invention.

Moreover, Applicants have pointed out in previous applications in the lineage herein the "unexpected results" demonstrated by the present application and have compared those unexpected results to the results of the collective Watson references. Applicants have pointed out that the present invention provides 100% effectiveness against the challenge of herpes simplex virus (HSV) at 100 to 500 times LD_{50}, whereas the fusion polypeptides of the Watson '315 patent provided only 30 to 80% survival against the challenge of 10 to 17 times LD_{50}. Applicants have argued, we believe with correctness, that these were unexpected results clearly evidencing the non-obviousness of the presently claimed invention.

In regard to the unexpected nature of the results presented herein, the is directed to page 28 and 31 of the present specification, Tables 1 and 2, where it is clearly shown that the truncated antigen provides complete effectiveness after immunization followed by challenge. Of the 11 mice treated, 11 survived and zero were dead. Of the control mice, three were paralyzed, seven were dead and three

survived. It was stated that the significance of this data stood at the $p=0.002$ level. Similarly in a second study represented by Table 2, again the vaccine of the present invention provided a 100% protection against challenge, the necessity of a vaccine.

Similarly on page 20 of the specification where mice were immunized with the full-length vaccine of the present invention, all of the mice in the control group died while all of the experimental mice were protected and showed no sign of infection. Thus, the specification itself fully supports the unexpected results of the present invention by this data alone. Applicants iterate that for a vaccine to be truly a vaccine, it must provide 100% protection. Contrast this with the data of the '315 Watson reference where they achieved no more than 80% protection with far less LD_{50} challenge, surely results defining failure as a vaccine. Thus, Applicants have herein provided an effective vaccine, something that the Watson art has failed to demonstrate.

Moreover, Applicants believe that a review of what the Watson researchers themselves actually thought of their experimental work would be instructive on the question of unobviousness. In this regard, we refer the to the subsequently published article by these researchers namely Weis et al., *Nature* 302:72-74 (1983), of record. The Watson (Weis) *Nature* reference represents a disclosure of a continuation of the earlier reported research in the cited Watson *Science* article. In the *Nature* article, the same authors describe the construction of a hybrid gene encoding again a chimeric protein, not a gD, not a truncated gD, containing HSV-1 gD, bacterial phage λCRO and E. coli β-galactosidase protein. They claim that the expedient of including the β-galactosidase portion provided higher levels of

expression of the chimeric product in E. coli. They go on to say that the chimeric protein elicits antibodies in rabbits to provide neutralization in vitro. It is emphasized that this does not amount to an in vivo challenge which is the premise of the present invention as embodied by the presently pending claims.

Turning to page 74, left column of the *Nature* article, in the only complete paragraph, it is interesting to note how the authors themselves characterize their work. They state, "[t]he results presented here demonstrate the feasibility of producing a sub-unit vaccine against HSV-1 and HSV-2 using recombinant DNA techniques." (emphasis supplied). Of course, that "feasibility" does not equate to success of actually producing an in vivo vaccine effective against challenge by virus.

Further down in the paragraph in the left column on page 74 of the *Nature* article, the authors indicate that the chimeric protein they produced was "capable of neutralizing...in vitro." Then they make the very telling admission that "[e]xperiments are now in progress to determine whether vaccination with the chimeric protein is capable of protecting experimental animals from HSV challenge." (Emphasis supplied). Thus, the very same authors themselves admit that it can not be predicted that their chimeric material would prove to be an effective vaccine.

Applicants believe this to be a telling comment by the very authors on which the Examiner bases her rejections. As we have noted herein, when the Watson authors finally did their challenge work, much later - see the '315 patent referred to earlier - they found at best 80% protection, a result clearly incapable of proving an

effective vaccine. Thus, while the Watson et al. authors would eagerly test their hypothesis, at the end of the day they did not achieve success as did the inventors of the present invention. We say that this itself is compelling evidence of unobviousness of the present invention in light of the collective Watson references.

With respect to the Examiner's comment on the data in Table 4 of the Watson '315 patent, we note, as pointed out above again, that the information set forth in that section of the patent entered the stream of priority via a continuation-in-part filed 6 July 1983. Therefore, the 37 C.F.R. Section 1.131 declaration serves to remove that material as a reference herein.

Secondly, and contrary to the Examiner's statement, particularly when considered in the light of two factors, namely, 1) the state of the art as of the effective filing date of the present application of August 1983 and 2) the state of uncertainty, even today, with respect to both vaccine production and efficacy, it could not have been predicted with reasonable certainty that a recombinant material, including the truncated form hereof (see Claim 10 hereof), could be expected to be made in sufficient quantities and produce efficacy as a vaccine to meet regulatory and commercial standards, i.e., 100% efficacy.

The Examiner states, erroneously of course, that the data set forth in our Tables 1 and 2 on pages 28 and 31, respectively, "show that the control mice survived and that the untreated mice did not survive." Probably this is an unintended misstatement. The data in our application clearly shows in Table 1 that the truncated version of the gD polypeptide made in accordance with the present invention gave 100% protection against challenge whereas of the control mice, 7 of

the 13 were dead by day 14, and 3 showed severe wasting and paralysis. Statistical analysis revealed that the difference between the immunized and control groups was significant at $p=0.002$.

Similarly in Table 2, 100% effectiveness was demonstrated in 15 mice with the gD truncated antigen of the present invention versus 0% survival of 25 control mice. In the Watson '315 patent, contrarily, levels of only 80% at most of survivors are demonstrated; it is not understood what the Examiner's reference is to an "irrelevant antigen". In addition, we note that Table 4 at least had protection with native material, a material not the product of a "foreign" production environment as are the recombinant vaccine products of the present invention.

With respect to Rose, in our previous response we indicated that the Rose gG protein of VSV was a truncated version and that the folding pattern of their material was such that it could be folded into "an unusual confirmation" thought to impede transport in the secretion model. (Page 760, left column). Our point was that, like the Watson '315 patent native material of Table 4, the present recombinant vaccines, being products of recombinant host cells, may be expected to be glycosylated and/or folded differently which could effect the immunogenicity of the final product. Thus, we said, Rose would support our position that the truncated material of the present invention, provided recombinantly as well, would not necessarily be expected to be completely immunogenic as is required by a vaccine.

Kaufman may teach essentially what the Examiner states but it has no bearing on the essential aspect of the present invention, namely, the preparation of a

vaccine useful for in vivo protection against herpes virus challenge after immunization.

In regards to Chan, Applicants again submit that the idea of a mixture does not bear on the essential aspect of the present invention. Moreover, Chan provides at best, a suggestion to investigate such mixtures, and provides no reasonable expectation that any of the glycoproteins would be effective as a vaccine against herpes.

With respect to the Examiner's comment about secondary considerations, and in particular the commercial success arguments made earlier, we point out that the Supreme Court of the United States has stated that "such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc. may be utilized to give light to the circumstances surrounding the origins of the subject matter sought to be patented." Graham v. John Deere Company, 148 U.S.P.Q. 459 (1966).

Further, the Federal Circuit has emphatically and repeatedly held that objective evidence of non-obviousness must be taken into account always and not just when the decision make is in doubt. See Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (C.A.F.C. 1986).

We have already propounded on the unexpected results of the present invention particularly in view of the collective Watson references which failed to achieve such results. The latter also emphasizes that while there were presumably any of a number of laboratories working on this product, the Applicants of the

present invention were the first to succeed with one that is currently enjoying developmental progress towards real commercialization.

The collective Watson references underscore the failure of others to achieve what the present Applicants have done towards the goal of commercial success. Further, we are aware that individuals working in the area were not able to successfully product a vaccine that would be sufficiently efficacious in order to prove commercialization. All of this is tantamount to the failure of others, a secondary indicia of patentability.

With respect further to our commercial success arguments, the Examiner's position that commercial success connotes large sales in the marketplace, we remind the record, again, that it takes years and great sums of money and the satisfaction of regulatory agents, *e.g.* the FDA, to achieve such in the marketplace. We mentioned and argued that the product of the present invention is in the process of commercialization - see the enclosed declaration Michel de Wilde originally filed in a parent application of the present invention on 2 September 1994 (Exhibit E). Certainly, the Examiner should not be permitted to simply ignore such concrete assertions of reality and require actual marketplace sales, when practicality dictates that one must satisfy a number of agencies beyond the purview of the Patent Office.

In summary, the prior art cited by the Examiner herein simply does not support the position that the results presented in the present application would be reasonably expected. Applicants have pointed out that the fusion polypeptides of the collective Watson references failed to give adequate protective results for purposes of producing and using a vaccine. Applicants also submit that the Rose art simply

underscores our position that it would be unexpected that a truncated version of a given antigen would be successful to provide 100% protection on challenge, i.e., an effective vaccine. Kaufman and Chan do not provide the missing elements of Watson and Rose required to arrive at the present invention. As such, the combination of the Watson art with Rose, Kaufman and Chan does not provide the suggestion or reasonable expectation of success required to support a rejection under 35 U.S.C. § 103. The rejection should, therefore, be withdrawn.

We believe that the above remarks serve to place the present application in an obvious condition of allowability, both as to formal matters and as to substantive matters based upon the prior art cited under 35 U.S.C. § 103.

Applicants wish to again remind the record of the substantial prosecution history of this application via the several patent applications in historical priority lineage with the present application. During the course of that prosecution which has already consumed many years, the substantive issues currently raised in Paper No. 8 have been previously raised, and we believe, completely and thoroughly rebutted, not only with legal arguments but with factual distinctions over the art upon which the rejections are based, coupled with the filing of several affidavits from persons of skill in the art of immunology as well as business officials who have attested to the secondary considerations that must be considered on questions of patentability.

We respectfully point to our belief that the record of the parent applications via the present application is already sufficiently developed so that one could not but

be led to a conclusion that patentable subject matter is certainly represented by the present claims.

Therefore, we respectfully request the review of such previous prosecution record, and by these remarks specifically incorporate by reference all of such prosecution history into the record of the present application. In particular we refer to the most immediate parent application hereof, U.S.S.N. 08/357,084 filed 15 December 1994 in which such prosecution was laboriously developed and filed including declarations by Drs. Skehel, Secher and Rose demonstrating factual evidence that established that at the time the present invention was made, scientific peers not associated with the inventors hereof could not have reasonably predicted success, but that after the fact of success of this invention as set forth in the present specification and claims, the invention was newly predictive of operability for similar type vaccine production over a wide pathogenic host range. The claims in this parent case have been allowed.

In addition, we have traced the history of vaccine development, reviewed the disclosure of the collective Watson references and provided distinctions that the present invention has over the publications used as the basis for substantive patentability rejections herein. We adduced evidence of secondary considerations mandatory for review in determinations on the issue of patentability. Moreover, we have presented convincing evidence in a Declaration under 37 C.F.R. § 1.131 that the present invention pre-dates the publications cited by the Examiner.

In addition, we forwarded the Decision of the Opposition Division of the European Patent Office for the European counterpart of the present invention

wherein said Opposition Division found for patentees on questions of novelty, obviousness and enablement. A copy of this Decision is enclosed herein as Exhibit F. We pointed out as well the judicial authority in this country that suggests that such decisions of foreign examining authorities should be taken as evidence probative on questions of patentability.

In short we have already adduced a copious review of the cited art and have summarized in considerable detail our arguments that we believe unequivocally establish patentability of the claimed subject matter. From all of this prosecution history we believe that it must be concluded that the review of patentability standards for the present claimed subject matter has been thorough and complete enough to induce the Patent Office's production of an official notice of allowance. We respectfully request this.

Respectfully submitted,

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